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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,347	01/19/2001	Raghavan Rajagopalan	MRD-60	7678

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EXAMINER
CEPERLEY, MARY

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/04/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,347	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	Mary (Molly) E. Ceperley	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *2-7 and 9-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1) Applicants' election with traverse of the invention of Group I, claims 1-10, further defined by Ar = phenanthridines, E = somatostatin receptor binding molecules, in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the compounds of claim 1 constitute a single invention for the reason that they share an organic azide structure and have utility as receptor-targeted azide derivatives and their bioconjugates for phototherapy of tumors and other lesions. This is not found persuasive because unlike the compounds described in *Weber* (cited by applicants), the Markush group of compounds of claim 1 do not possess a core common structure responsible for the disclosed utility. Considering *only* the moiety "Ar", for example, claim 1 includes compounds containing moieties as diverse as single 5-membered single nitrogen containing heterocycles, multicyclic oxygen containing heterocycles, benzene, 6-membered dinitrogen containing heterocycles, and sulfur containing rings, which moieties do not have a core structure in common. Indeed, a reference which would anticipate or render obvious compounds containing one definition of "Ar" would not necessarily render obvious another compound having a different definition of "Ar". Additionally, there is no description in the specification of any commonality in structure of the moiety "E". Page 12, lines 11-15 of the specification provides a list of possible definitions of "E", but does not establish any structural commonality for this group. A reference, for example, which would anticipate or render obvious a compound wherein "E" is defined as hydrogen would not necessarily render obvious the corresponding compound wherein "E" is defined as "cholecystekinin receptor binding molecule".

Claims 11-27 are withdrawn from further consideration as being drawn to non-elected inventions. Applicants have not specifically traversed the restriction requirement between the compound and method of use claims. Claims 2-7, 9, and 10 are withdrawn from further consideration as not being readable on the elected invention. Claims 1 and 8 are treated on the merits in this Office action to the extent that they encompass the compounds of claim 1 wherein "Ar" is defined as "phenanthridines" and "E" is defined as "somatostatin receptor binding molecules".

The requirement is still deemed proper and is therefore made FINAL.

2) Applicants are advised that in accordance with the court decisions in *In re Ochiai,* {71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995)} and *In re Brouwer* {77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996)}, in the event that a product claim is found to be allowable, a method of use claim ***which is of the same scope as the allowed product claim*** may be rejoined with the allowed product claim.

3) Claims 1 and 8 are rejected under judicially created doctrine as being drawn to an improper Markush group for the reasons stated in paragraph ***1)*** above.

4) The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6) Claims 1 and 8 are rejected under 35 USC 112, second paragraph, as being indefinite and/or confusing for the following reasons.

a) The claims are indefinite in the use of the term "derived from...phenanthridine***s***" used as a definition of "Ar". It is unclear what is meant to be encompassed by this term. This term does not adequately specify the minimum required structure nor the nature and number of other substituents and/or multiple rings which may be implied by the plural designation. In the March 10, 2003 response, applicants state at page 9, that the recited definitions of "Ar" refer to "the family of compounds". However, the specification fails to define any such "family" and in the absence of any such guidance, it is unclear what is meant to be included by the claim language.

b) It is unclear what is meant to be encompassed by the term "E" defined as "somatostatin receptor binding molecules". Page 14, line 3 of the specification indicates that "somatostatin" *per se* is a "somatostatin receptor binding molecule" but it is unclear that the term "somatostatin receptor binding molecules" represents an art recognized term that includes any compound *other than* "somatostatin".

c) In the absence of an indication of where the moieties "L" and "X" connect to the moieties "E" and "Ar", the exact structure of the compounds encompassed by the formula of claim 1 is unclear. Applicants' assertion at page 7 of the March 10, 2003 Remarks that the attachment points of the various groups to each other "is not the claimed invention" does not address the issue under 35 USC 112, second paragraph, that the claims must "particularly point out and distinctly claim the invention". In return for a grant of patent rights, the public must be advised of exactly which compounds are covered by the patent claims; no such determination can be made for claims 1 and 8.

d) In claim 8, it is unclear what is meant by the term "Ar is *an aromatic* or heteroaromatic radical derived from phenanthridines" since "phenanthridine" is a "heteroaromatic" moiety.

7) Claims 1 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There is no enablement in the specification for how to prepare the elected compound wherein "Ar" is "phenanthridines" and "E" is "somatostatin receptor binding molecules". Although Figure 6 describes the reaction of a known, specific 8-azidoethidium (phenanthridine) compound to form the –NCS derivative, it is not clear that the "somatostatin receptor binding molecule" has the requisite amine group necessary for reaction nor how such an amine group would be introduced into the "somatostatin receptor binding molecule".

8) Claims 1 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the preparation of all compounds which correspond to the

structure of claim 1 wherein "E" is "somatostatin receptor binding molecules" and "Ar" is "phenanthridines". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There is no enablement for how to prepare any compound other than through the intermediate compound depicted in Figure 6 wherein "L" is a bond {-$(CH_2)_0$-} and "X" is a single bond.

9) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10) Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by each of Graves (Advances in DNA Sequence Specific Agents (1996), ***2***, 169-186), Yielding et al (Biopolymers (1984), ***23***, 83-110), and Ito et al (Langmuir (1997), ***13***, 2756-2759).

Graves describes the compound 8-azidoethidium bromide (*Figure 1*) which anticipates the compound of claim 1 wherein "Ar is...a radical derived from...phenanthridines", "L" = -$(CH_2)_0$-, "E" = hydrogen, and "X" is a single bond. See also, Figure 6 of the instant application.

Yielding et at describe 8- and 3-azidoethidium derivatives (TABLE I) which anticipate the compound of claim 1 wherein "Ar is...a radical derived from...phenanthridines", "L" = -$(CH_2)_0$-, "E" = hydrogen, and "X" is a single bond.

Ito et al describe 4-azidoaniline (Figure 1. a) which anticipates the compound of claim 1 wherein "Ar is...a radical derived from...benzenes", "L" = -$(CH_2)_0$-, "E" = hydrogen, and "X" is a single bond.

This rejection does not imply that a full search has been made of the complete Markush group of claim 1.

11) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12) Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over ***a)*** Molecular Diagnostics (EP 187,332) taken in combination with ***b)*** the admitted prior art.

Molecular Diagnostics describes a conjugate comprised of the known ligand/receptor, biotin, and the known photolabeling agent, 8-azido ethidium (see page 26, MD 223; the second structure of page 17), which is useful in a ligand-receptor binding assay. Page 15, line 35 through page 16, line 3 describe the biological targeting function of the biotin moiety (i.e. ligand-receptor) of the conjugate and the photochemical reactivity of the photolabel (e.g. phenanthridinium of page 17). Molecular Diagnostics further describes a wide variety of equivalent ligands/receptors which are useful conjugate components. See page 14, line 19 through page 15, line 23. The reference does not specifically describe the use of a "somatostatin receptor binding molecule" as a ligand/receptor.

The admitted prior art as set forth at page 13, line 18 through page 14, line 13 of the instant specification establishes that a wide variety of ligands/receptors, including somatostatin (a "somatostatin receptor binding molecule"), are well known in the art as complementary targeting agents.

In view of the fact that somatostatin/somatostatin receptor is a well known ligand/receptor targeting combination (the admitted prior art), it would be obvious to substitute one well known ligand/receptor, i.e. somatostatin/somatostin receptor, for the equivalent ligand/receptor biotin in the conjugate of Molecular Diagnostics, as claimed, with the expectation of obtaining a similarly useful conjugate for targeting to the corresponding member of the ligand/receptor binding pair.

13) Claims 1 and 8 are rejected under 35 USC 103(a) as being obvious over ***a)*** Cryopharm (WO 93/14791) taken in combination with each of ***b)*** Pelegrin et al (J. Cell Pharmacol (1992), ***3***, 141-145), Jori [A] (J. Photochemistry and Photobiology B (1996), 87-93), or Jori [B] (J. Photchem. Photobiol. (1992), **62**, 371-378) and ***c)*** further in combination with the admitted prior art.

Cryopharm describes a wide variety of known photosensitive agents, including 8-azido ethidium, which are useful in biological targeting. See page 19, the second structure of lines 21-25; page 20, lines 19-27; page 21, lines 1-4; page 36, lines 11-14.

References ***b)*** establish that it is well known to conjugate photosensitive agents with targeting ligands to provide *in vivo* localizing of the photosensitive agents. See Pelegrin et al, page 141, first seven lines; Jori [A], Table 3; Jori [B], abstract and page 376, the second paragraph under paragraph 5.

The admitted prior art as set forth at page 13, line 18 through page 14, line 13 of the instant specification establishes that a wide variety of ligands/receptors, including somatostatin (a "somatostatin receptor binding molecule"), are well known in the art as complementary targeting agents.

In view of the fact that somatostatin/somatostatin receptor is a well known ligand/receptor targeting combination (the admitted prior art), it would be obvious to substitute one well known ligand/receptor, i.e. somatostatin/somatostin receptor, for the equivalent ligand/receptor component in the photosensitive agent-targeting ligand conjugates of references ***b)***, as claimed, with the expectation of obtaining a similarly useful conjugate for the *in vivo* targeting of the known photosensitive agent, 8-azido ethidium.

14) Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. (Molly) Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached at (703) 305-3399. The fax phone number for responses to be filed BEFORE

final rejection is (703) 872-9306. The fax phone number for responses to be filed AFTER final rejection is (703) 872-9307.

Questions which are NOT RELATED TO THE EXAMINATION ON THE MERITS, should be directed to **TC 1600 CUSTOMER SERVICE at (703) 308-0198**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

May 29, 2003

Mary E. Ceperley

Mary E. (Molly) Ceperley
Primary Examiner
Art Unit 1641